CHAPTER 15
CALCIUM SIGNALLING AND CANCER CELL GROWTH

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Abstract: Cancer is caused by defects in the mechanisms underlying cell proliferation and cell
death. Calcium ions are central to both phenomena, serving as major signalling agents
with spatial localization, magnitude and temporal characteristics of calcium signals
ultimately determining cell’s fate. There are four primary compartments: extracellular
space, cytoplasm, endoplasmic reticulum and mitochondria that participate in the cellular
Ca2+ circulation. They are separated by own membranes incorporating divers Ca2+-
handling proteins whose concerted action provides for Ca2+ signals with the spatial and
temporal characteristics necessary to account for specific cellular response. The trans-
formation of a normal cell into a cancer cell is associated with a major re-arrangement of
Ca2+ pumps, Na/Ca exchangers and Ca2+ channels, which leads to the enhanced prolif-
eration and impaired ability to die. In the present chapter we examine what changes in
Ca2+ signalling and the mechanisms that support it underlie the passage from normal to
pathological cell growth and death control. Understanding this changes and identifying
molecular players involved provides new prospects for cancers treatment

Keywords: Apoptosis, proliferation, calcium channels

1. INTRODUCTION

Cancer is caused by defects in the mechanisms underlying cell proliferation and
cell death. The development of tumours results from excessive cell proliferation
combined with inhibition of cell apoptosis that eventually leads to imbalances in
tissue homeostasis and uncontrolled growth. The molecular machineries of prolif-
eration and apoptosis are different, with proliferation relying on cyclin-dependent
protein kinases (CDKs) – regulators of cell division cycle (Nigg, 1995) – and
apoptosis primarily dependent on caspases – cysteine proteases executing a cell
death programme (Nicholson, 1999). Nevertheless, calcium ions are central to both
phenomena, serving as major signalling agents. From these observations, it is clear

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that changes in cytosolic free calcium ([Ca$^{2+}$]$_i$) alone are insufficient for governing such diverse processes deciding cell fate. Therefore, the amplitude, spatial localization and temporal characteristics of calcium signals are of major importance in determining death, survival and proliferation (Berridge, 1995, Berridge, et al., 1998, Kahl, et al., 2003, Lipskaia, et al., 2004, Munaron, et al., 2004, Orrenius, et al., 2003). Enzymatic reactions and gene activation obviously occur in the cytoplasm and nucleoplasm, and there is recent unequivocal evidence that calcium levels within the endoplasmic reticulum (ER) and mitochondria are at least as important as [Ca$^{2+}$], changes. The formation of local signalling complexes due to restricted calcium diffusion (Allbritton, et al., 1992) may well allow even greater specialization of the cellular responses controlled by this divalent cation.

Cell transition from the normal to the malignant state is a multistage process characterized by a major reorganization of the molecular machinery of active and passive Ca$^{2+}$ transport across cellular and subcellular membranes, and also Ca$^{2+}$ buffering, accumulation and extrusion by various intracellular organelles (Berridge, et al., 2003). In this chapter we outline the major mechanisms of Ca$^{2+}$ signalling and examine their involvement in the control of cell death and proliferation. However, the relationships to cancer development are not always straightforward and direct comparisons of normal and tumour cells are rare; indeed, cell lines have been widely used to understand some of the processes leading to abnormal cell proliferation.

2. **EXTRACELLULAR CALCIUM AND CANCER**

Extracellular Ca$^{2+}$ is essential for a number of vital processes as diverse as bone formation and muscle contraction. The G protein-coupled Ca$^{2+}$-sensing receptor (CaSR) can sense extracellular Ca$^{2+}$ concentration ([Ca$^{2+}$]$_o$) over the range of 0.05–5 mM, which makes it a key mediator of cellular responses to physiologically relevant changes in extracellular Ca$^{2+}$ (Msaouel, et al., 2004). It is an essential component of the homeostatic system regulating parathyroid hormone secretion, Ca$^{2+}$ excretion by kidney, and bone remodeling. For many cell types, including intestinal epithelial cells, breast epithelial cells, keratinocytes, and ovarian surface epithelial cells, changes in [Ca$^{2+}$]$_o$ in the 0.05–5 mM range can switch cellular behaviour from proliferation to terminal differentiation or quiescence. As cancer is the consequence of a disordered balance between proliferation, differentiation, and apoptosis, disruption of the function of the CaSR is a likely contributor (Rodland, 2004). Loss of the growth suppressing effects of elevated extracellular Ca$^{2+}$ have been demonstrated in parathyroid hyperplasias and in colon carcinoma, and have been correlated with changes in the levels of CaSR. Diminished CaSR expression results in abnormal differentiation and progression of colorectal carcinoma. For instance, the human colon adenocarcinoma-derived cell line, Caco-2, responds to low ambient [Ca$^{2+}$]$_o$ by activation of the protein kinase C-signalling pathway ultimately leading to upregulation of c-myc mRNA production and release from the G1/S phase control of the cell cycle (Kallay, et al., 2000). This proliferative response can be abolished by activation of CaSR either through raising [Ca$^{2+}$]$_o$ or by using